REMARKS

In view of the following remarks, the Examiner is respectfully requested to withdraw the rejections and allow Claims 17-26, as well as newly added claims 41 to 70, the only claims pending and under examination in this application following entry of the above amendments.

With respect to the claim number, the front page of the office action lists claims 1-47 as pending. However, only claims 1 to 40 are believed to have been pending when the office action was issued, claims 41 to 47 not having yet been presented until the present response.

With respect to new claims 41 to 70, these claims find support in the claims as originally filed, as well as in the specification. See particularly paragraphs 74 to 80. Accordingly, the above new claims introduce no new matter to the application and their entry by the Examiner is respectfully requested.

Objection to the Specification

The specification is objected to on the grounds that documents have been improperly incorporated by reference. The Examiner objects to the language at pages 21, 22, and 23 relating to the incorporation by reference of all patents, patent applications and publications mentioned in the application. The Examiner asserts that the language "fails to specify what specific information applicant seeks to incorporate by reference and similarly fails to teach with detailed particularity just where that specific information is to be found in each of the cited references." The Applicants note that the documents cited in the instant application are incorporated by reference in their entirety and are not limited to specific portions or passages thereof.

In making this objection, the Examiner relies on *Advanced Display Systems*. As is demonstrated below, the Applicants respectfully submit that the cited case law cited in the Office Action is mischaracterized and does not, in fact, stand for the general principle alleged in the Office Action. Accordingly, the Applicants thus

respectfully submit, as supported by the discussion below, that the instant situation is not analogous to that of *Advanced Display Systems, Inc.* Furthermore, the Applicants respectfully submit that the manner in which the documents of the instant application are incorporated by reference are proper and thus the documents cited in the present application are properly incorporated by reference in their entireties.

The Office Action relies on *Advanced Display Systems, Inc.*, to support a general proposition that the specification must identify specific portions of a document incorporated by reference. The relevant issue in *Advanced Systems* concerned anticipation based not on a patent alone, but rather on the combination of the patent and the material potentially incorporated by reference therein. The issue thus was whether a magistrate judge committed legal error by instructing the jury to determine whether and what material was incorporated by reference into the patent. The court described generally the subject of incorporation by reference. In this description, the court noted "To incorporate material by reference, the host document must identify with detailed particularity what specific material it incorporates and clearly indicate where that material is found in the various documents. See *In re Seversky*, 474 F.2d 671, 674, 177 U.S.P.Q. (BNA) 144, 146 (CCPA 1973) (providing that incorporation by reference requires a statement "clearly identifying the subject matter which is incorporated and where it is to be found")". It is this passage that the Office Action cites.

However, the situation of *In re Seversky*, the case cited in *Advanced Display*, is wholly different from the present situation. In the situation of *In re Seversky*, the Appellant attempted to incorporate by reference teachings of interest from a grandparent application. The parent application, was totally devoid of any reference to the teachings of interest, however the Appellant urged that the defect was cured because the grandparent disclosed the teachings and because the parent application is a continuation-in-part of the grandparent that disclosure was, *ipso facto*, incorporated by reference in the parent. In other words, the situation was one in which there was no "incorporation-by-reference" language whatsoever - a situation

wholly different from the instant application which does include "incorporation-by-reference" language.

Accordingly, the Applicants submit that the documents cited in the instant application are properly incorporated by reference in their entireties. As such, the Applicants respectfully request the objection to the specification be withdrawn.

Rejection under 35 U.S.C. § 112, first paragraph – Written Description

Claims 17-26 have been rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking written description. This rejection is respectfully traversed.

In making this rejection, the Examiner asserts in paragraph 5 of the office action that the claimed method reads as "encompassing the production of microarrays where virtually any ligand, be it DNA, RNA, antibodies, antigens, hormones, steroids, etc., are spotted in an array format on the treated substrate ... [and] as resulting in virtually and [sic] density of array spots, as well as any density of ligand at any given position."

In support of this position the Examiner in paragraph 6 cites U.S. Patent No. 5,858,671 and asserts that certain art-recognized areas of difficulty exist, such as the obstacle in synthesizing oligonucleotide arrays. The Examiner further stresses that the specification "does not provide an adequate written description as to how these art-recognized difficulties are to be overcome" (Office Action, paragraph 7).

The law is clear that, if a person of ordinary skill in the art would have understood the inventor to have been in possession of the claimed invention at the time of filing, even if not every nuance of the claims is explicitly described in the specification, then the adequate written description requirement is met.[1] Further, "an applicant ...is generally allowed claims, when the art permits, which cover more than the specific embodiment shown."[2]

1 *In re Alton* 76 F.3d 1168, 37 USPQ2d 1578 (Fed. Cir. 1996).
2 *Ethicon Endo-Surgery, Inc. v. United States Surgical Corp.*, 93 F.3d 1572, 40 USPQ2d 1019 (Fed.

As provided in the specification on page 9, paragraph [0045], the subject methods provide:

> in general terms, coating a substrate surface with a polyelectrolyte layer, and stably associating, e.g., covalently bonding, the polyelectrolyte layer to the substrate surface. More specifically, the method includes treating or contacting the polyelectrolyte-coated substrate surface with a bifunctional molecule having a first moiety that passivates, e.g., by covalently bonding to, the polyelectrolyte layer, and a second moiety that stably associates with, e.g., covalently bonds to, the substrate surface. By "stably associates with" is meant that the film is immobilized on the substrate surface during standard hybridization, washing and visualization conditions, where the film does not deadsorb from the substrate surface under these conditions. In many embodiments, the bifunctional molecule, in other words, is an agent or reactant having at least one functional group capable of covalently bonding to the polyelectrolyte coating and at least one functional group capable of covalently bonding to the substrate surface itself. The method also comprises subjecting the substrate and polyelectrolyte layer to a condition or conditions suitable to effect covalent bonding of the bifunctional molecule to the polyelectrolyte film and to the substrate surface.

Moreover the specification also provides on page 24, paragraph [0085] that:

> The covalent bonding of the polyelectrolyte layer to the substrate surface as provided by the invention prevents deadsorption or deformation of the polyelectrolyte layer which could otherwise occur during hybridization or other reaction with the nucleic acid spots on the polyelectrolyte layer.

The Applicants maintain that the specification provides adequate written description support for such a disclosure. In particular, the Applicants respectfully submit that the specification provides abundant written description support for practicing the claimed invention. In particular, the Applicants note that the specification provides support for selecting a substrate appropriate for use in the subject methods at, for example, pages 11 through 13; support for selecting an appropriate polyelectrolyte material for layering on the substrate surface at, for

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Cir. 1996).

example, pages 13 through 14; and support for selecting the bifunctional molecule for covalently the polyelectrolyte layer to the substrate surface.

Moreover, the specification also provides abundant written description support for methods for fabricating an array, such as, preparation of polymeric ligands is described, for example, in paragraphs [0075] and [0076] on page 20; preparation of aqueous solvent is described, for example, in paragraph [0077] on page 21; contacting of the aqueous polymer composition with the surface is described, for example, in paragraph [0078] on page 21, and the resulting immobilization of the ligands on the polyelectrolyte layer on the substrate surface is described at, for example, paragraph [0079] on pages 21 and 22.

Furthermore the specification provides working examples demonstrating the methods of the present invention in the coating of a substrate surface (Example 1), preparation of nucleic acid probe spots on the coated surface (Example 2), and successful use of the microarrays in mock hybridization conditions (Example 3).

As noted by the Examiner in the Office Action, the pending claims are not limited to particular type of ligand, e.g., nucleic acid, but encompass different types of ligands as well as various densities of the ligands on the array surface. The Applicants maintain that by showing fabrication of a microarray with a particular type of ligand (nucleic acid, see Example 2), the Applicants have established that the claimed method of fabricating a microarray would be successful with other types of ligands. There is no reason to believe that depositing one type of ligand on an array surface would be different than another type of a ligand. In support, the Applicants note that several U.S. Patents have issued with a similar scope with respect to the type of ligands that may be deposited on the array surface (see, for example, 6,087,102; 6,110,426; 5,685,734). In addition, the Applicants note that several U.S. Patents have issued with a similar scope with respect to density of the ligands on the array surface (see, for example, 5,624,711 and 5,445,934). Accordingly, there is no reason to believe that various densities of ligands could not be successfully arrayed on the array surface according to the claimed method.

In view of the above, it is submitted that the claims do comply with the written description requirement in that the claims are directed to methods of fabricating a microarray. The specification provides multiple representative examples, including working examples, of representative background features being employed in the claimed methods, such that one of skill in the art would have no doubt that the applicant was in possession of the invention as claimed at the time the application was filed.

Rejection under 35 U.S.C. § 112, first paragraph – Enablement

Claims 17-26 have been rejected under 35 U.S.C. §112, first paragraph, as based on a specification that allegedly fails to enable one skilled in the art to make and use the invention. In support of this rejection, the Examiner asserts that various aspects of the specification support this rejection such as a lack of working examples. The Examiner further states that the specification does not provide any guidance as to how issues related to ligand density or length of ligands can be addressed. This rejection is respectfully traversed.

As noted in the Office Action, a specification complies with the statute even if a reasonable amount of experimentation is required, as long as the experimentation is not "undue". One way to determine if undue experimentation is required is to utilize the *Wands* factors: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims." All of the factors need not be reviewed when determining whether a disclosure is enabling.[3]

3 See *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1213, 18 USPQ2d 1016, 1027 (Fed. Cir. 1991).

The Applicants respectfully submit that when evaluated in view of the relevant *Wands* factors, the specification clearly enables one of skill in the art to practice the subject invention without undue experimentation. In other words, Claims 17-26 contain subject matter which is adequately described in the specification in such a way to teach someone how to make and use the claimed invention without having to practice undue experimentation. An analysis of the relevant *Wands* factors is provided below.

(1) the quantity of experimentation necessary

The Applicants respectfully submit that the quantity of experimentation required to practice the subject invention is reasonable. The courts have clearly taught that the fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. For example, see MPEP §2164.01.[4] As the court explained:

> [A] considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.[5]

Practitioners in the chemical and molecular biology arts frequently engage in extensive modification of reaction conditions and complex and lengthy experimentation where many factors must be varied to succeed in performing an experiment or in producing a desired result. The Federal Circuit has found that such extensive experimentation is not undue in the molecular biology arts. For example, the court concluded that extensive screening experiments, while being voluminous, were not undue in view of the art which routinely performs such long experiments.

> The claimed compositions recite isolated polypeptides with 60% or more sequence identity to SEQ ID NO:3 that suppress proliferation of lympho-hematopoietic cells. The only experiments, if any, that need be performed to enable the entire scope of the claim are those designed to determine which

4. See also *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), *aff'd sub nom., Massachusetts Institute of Technology v. A.B. Fortia*, 227 USPQ 428 (Fed. Cir. 1985).
5. *In re Wands* 8 USPQ 2d at 1404.

> sequences retain the ability to suppress proliferation of lympho-hematopoietic cells. The sequence of polypeptides retaining biological activity is determined through routine experimentation that is empirical in nature, typically employing nothing more than performing the same assay disclosed in the specification on a variety of sequence variants of the polypeptide made by routine recombinant DNA techniques. Since these experiments are empirical in nature, no undue experimentation is required. In other words, the only experimentation that may be required to enable the claimed invention are those experiments to determine the presence of a certain activity, and since this only requires a routine assay on polypeptide variants to determine the active variants, no undue experimentation is necessary.[6]

The claims of present application are directed to methods for fabricating a microarray by depositing ligands on a polyelectrolyte layer on the surface of a substrate. As provided below, the Applicants maintain that the specification provides ample disclosure to enable one skilled in the art to practice the claimed invention. For example, preparation of polymeric ligands is described, for example, in paragraphs [0075] and [0076] on page 20; preparation of aqueous solvent is described, for example, in paragraph [0077] on page 21; contacting of the aqueous polymer composition with the surface is described, for example, in paragraph [0078] on page 21, and the resulting immobilization of the ligands on the polyelectrolyte layer on the substrate surface is described at, for example, paragraph [0079] on pages 21 and 22. Therefore, in view of such guidance provided in the specification, in combination with the knowledge of one of skill in the art, and experimentation that may be necessary is reasonable.

The Examiner also stresses that "the specification does not address issues of ligand density or length of ligands where one ligand could form hairpin structures with itself, or hybridize with adjacent members of the array" (Office Action, paragraph 13). With respect to the technical concerns raised by the Examiner, the Applicants note that the field of microarray fabrication is sufficiently well developed that solutions to such technical concerns could be readily addressed without undue and excessive experimentation.

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6. *Hybritech v. Monoclonal Antibodies, Inc.* 231 USPQ 81 (Fed. Cir. 1986)

In support, the Applicants note that several U.S. Patents have been issued in the microarray fabrication field that have addressed the same technical concerns raised by the Examiner. For example, 5,400,637 (Southern et al., issued Dec. 23, 1997) discloses methods of fabricating an array by depositing nucleic acids on a solid support; 5,658,734 (Brock et al., issued August 19, 1997) discloses methods for synthesizing on a single substrate a plurality of chemical compounds having diverse structures; 5,624,711 (Sundberg et al., issued April 29, 1997) discloses methods for phase synthesis of peptides, oligonucleotides or other small organic molecules, and arrays or ligands, as well as controlling functional site density on a solid support; 5,436,327 (Southern et al., issued June 25, 1997) discloses methods for synthesizing oligonucleotides on a solid support; 5,445,934 (Fodor et al., issued August 29, 1995) discloses methods of fabricating array of oligonucleotides on a solid support at various densities; 6,087,102 (Chenchick et al., issued July 11, 2000) discloses methods or fabricating arrays of polymeric targets stably associated with the surface of a solid support; and 6,110,426 (Shalon et al., issued August 29, 2000) discloses methods for forming microarrays of biological samples on a support. Accordingly, since the knowledge in the relevant field of microarray fabrication is high, as evidenced by the large number patents and publications, the technical concerns raised by the Examiner could be readily addressed by one of skill in the art without undue and excessive experimentation.

Accordingly, the Applicants respectfully submit that the specification and the amended claims, coupled with the information available in the relevant art, one of skill would be able to practice the claimed invention without undue and excessive experimentation.

(2) the amount of direction or guidance presented

The claims of the present invention are directed to methods for fabricating a microarray by producing a polyelectrolyte layer on a substrate surface, depositing a plurality of spots of ligands on the polyelectrolyte layer, and contacting the polyelectrolyte layer with a reagent to produce a covalent bond. As noted above, the

specification provides ample support for such recitations, for example at pages 13-16 and pages 19-22.

Moreover, the specification details the variety of substrates that may be used in the subject methods for fabricating an array at, for example, page 11, paragraph [0052] through page 13, paragraph [0056]. The noted section also discusses representative modifications that can be made to the substrate surface prior to depositing the polyelectrolyte layer on the surface (See, for example, page 12, paragraph [0055]).

Finally, the specification also provides abundant description for methods of fabricating an array. For example, preparation of polymeric ligands is described in paragraphs [0075] and [0076] on page 20; preparation of aqueous solvent is described, for example, in paragraph [0077] on page 21; contacting of the aqueous polymer composition with the surface is described, for example, in paragraph [0078] on page 21, and the resulting immobilization of the ligands on the polyelectrolyte layer on the substrate surface is described at, for example, paragraph [0079] on pages 21 and 22.

Accordingly, for at least the reasons described above, the Applicants respectfully submit that the specification provides ample guidance and direction to the practice the claimed invention.

(3) the presence or absence of working examples

Compliance with the enablement requirement under Title 35 U.S.C. §112, first paragraph does not require or mandate that a specific example be disclosed. The specification need not contain a working example if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice the invention without undue experimentation.[7] Furthermore, "[n]othing more than

7. *In re Borkowski*, 164 USPQ at 645.

objective enablement is required, and therefore it is irrelevant whether [a] teaching is provided through broad terminology or illustrative examples.'"[8]

As noted by the Examiner in the outstanding Office Action, the present application does contain working examples demonstrating the methods of the present invention in the coating of a substrate surface (Example 1), preparation of nucleic acid probe spots on the coated surface (Example 2), and successful use of the microarrays in mock hybridization conditions (Example 3). As such, the present application does provide a person skilled in the art, through the specification as well as the working example, sufficient enablement to fabricate a microarray according to the subject methods of the present invention.

Moreover, the Applicants note that the presence or absence of working examples is but one factor to be taken into consideration in determining whether the specification is enabling for the full scope of the claims. Under MPEP § 2164.02 the consideration is whether one skilled in the art would be expected to be able to extrapolate the provided examples across the entire scope of the claim. As presented herein, Applicants argue that it would be reasonable to conclude that one skilled in the art would be able to extrapolate the working examples provided in the specification across the across the entire scope of the claims without excessive and undue experimentation. As such, based on the disclosure provided in the application one skilled in the art would be able to extrapolate the working examples, to the use of any ligand, as described in the specification, not nucleic acids.

(4) the nature of the invention

The nature of the invention is generally directed towards depositing a plurality of spots of ligands on a polyelectrolyte layer, which polyelectrolyte layer is on a surface of a substrate, in order to fabricate a microarray. Therefore, such methods may generally encompass solid phase chemistry and specifically chemical or biochemical reactions on a surface. As such, the nature of the invention typically involves experimental research that may include detection and/or analyzing

8. *In re Robins* 166 USPQ 552 at 555 (CCPA 1970).

biomolecular components. Accordingly, the nature of the invention is that practitioners of this art are prepared to perform experimental research. As such, when viewed in light of the ample guidance provided by the specification, the state of the art, the high relative skill of those in the art, etc., the amount of experimentation, if any, needed to practice the subject invention is not excessive.

(5) the state of the prior art

The subject invention is concerned with fabricating a microarray by depositing a plurality of spots of ligands on a polyelectrolyte coated surface of a solid support. Accordingly, the subject invention relates to fabricating a microarray in general and specifically chemical and biochemical reactions on a substrate surface. As noted above the state of the art with respect to fabricating a microarray is sufficiently well developed as evidenced by the numerous publications and issued patents in the relevant filed of fabricating microarrays. As evidence of such, the Applicants point to at least to the U.S. Patents cited above, which detail the developed state of the art of array manufacturing (see, for example, 5,400,637; 5,658,734; 5,624,711; 5,436,327; 5,445,934; 6,087,102; and 6,110,426). As such, the Applicants maintain that the state of the art is well developed such that one skilled in the art would be able to readily address any technical concerns.

(6) the relative skill of those in the art

There is a high level of skill of those in the art who practice the present invention. Typically, practitioners of the art or fabricating a microarray are highly skilled in fields such as the biological and physical sciences and the like and typically possess advanced degrees. Accordingly, one skilled in the relevant art would be capable of addressing the technical concerns that the Examiner specifically raised in the Office Action.

(7) the predictability or unpredictability in the art

The subject invention is concerned with fabricating a microarray by depositing a plurality of spots of ligands on a polyelectrolyte coated surface of a solid support.

As such, the subject invention pertains to the field of fabricating microarrays, the art of which is not as unpredictable as the Examiner asserts.

The Applicants note that the field of fabricating microarrays is sufficiently well developed; therefore it is not an unpredictable art. For example, as provided above, the Applicants note that several patents have issued in the relevant field of microarray fabrication. For example, representative patents in the microarray field include: methods for fabricating an array by depositing nucleic acids on a solid support (5,400,637); methods for synthesizing a plurality of chemical compounds on a single surface (5,658,734); methods for synthesizing oligonucleotides on a solid support (5,436,327); methods or fabricating arrays of polymeric targets (6,087,102); and methods for forming microarrays of biological samples on a support (6,110,426).

Moreover, by reporting the successful fabrication of a microarray using the subject method, the Applicants maintain that the field is not as unpredictable as asserted by the Examiner. In sum, armed with the teachings provided in the specification, the Applicants stress that the field is not so unpredictable. One could practice the full scope of the claimed invention without undue experimentation.

(8) the breadth of the claims

The claims of the instant application encompass methods for fabricating microarrays by producing a polyelectrolyte layer on a substrate surface, depositing a plurality of spots of ligands on the polyelectrolyte layer, and contacting the polyelectrolyte layer with a reagent to produce a covalent bond. As noted above, the specification provides ample support for such recitations, for example at pages 13-16 and pages 19-22. As such, the specification provides the requisite enablement for a person of skill in the art to make and practice the invention to the full scope of the pending claims.

In sum, the amount of experimentation required to fabricate a microarray using the subject methods would not be undue and excessive because working examples have been provided, guidance is given on how to fabricate the microarray,

and one of skill in the art would be able to perform the experiments as a matter of routine. The specification therefore provides sufficient enablement such that one of ordinary skill in the art would be able to practice the invention without undue experimentation. Accordingly, the specification clearly enables the subject invention as demonstrated in view of the relevant *Wands* factors.

As such, for at least the reasons described above, Claims 17-26 are adequately enabled by the specification. Accordingly, the Applicants respectfully request that the rejection of Claims 17-26 under 35 U.S.C. §112, first paragraph be withdrawn.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: September 30, 2004

By: _____
Bret E. Field
Registration No. 37,620

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